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Diagnostic and Treatment Delays in Penile Cancer: A Call to Improve Awareness and Referral

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Abstract

Introduction: In men with penile cancer (PeCa), timely referral is crucial for optimizing clinical outcomes. We investigated the association between time from initial presentation to first surgical treatment and its effect on patient outcomes.

Material and methods: Data from a single center prospectively maintained database of patients with PeCa who underwent primary surgery between 2010 and 2024 were analyzed, excluding those treated elsewhere. We assessed time intervals from initial disease appearance to referral across general practitioners (GP), urology or dermatology specialists (SP), and our center. We also compared disease characteristics, surgical approach, and oncological outcomes among patients referred before or after 12 months from disease appearance.

Results: Overall, 48 patients were included. Median (IQR) time from presentation to our center was 12.4 (6.8-25.4) months. Referral pathways included: 13 (27%) patients were referred through GP, SP and our center [median time to treatment 13.9 (9.7-20.4)], 8 (17%) were directly referred by the GP to our center [18.2 (9.1-26)], 10 (21%) saw the SP first and were then referred to our center [6.8 (6.1-10.5)], and 17 (36%) went directly to our center [14.3 (11-24.8)]. Overall, 28 (58.3%) (Group 1) and 20 (41.7%) (Group 2) patients were surgically treated before or after 12 months of disease presentation, respectively. In Group 1, pT stage and lymphovascular invasion were significantly lower (both $P \leq 0.02$). Surgery after 12 months was associated with higher risk of recurrence [OR 4.28 (CI 1.26, 22.5); P=0.03] and lower 2-year recurrence free-survival (33.8% vs. 84%; P=0.005).

Conclusion: Even in a high-income country, the median time from the initial presentation of PeCa to a tertiary center is alarmingly prolonged. This delay is associated to more advanced disease at treatment and potentially worse oncological outcomes. Raising public awareness about PeCa and establishing streamlined, dedicated referral pathways should be prioritized as essential strategies.

INTRODUCTION

Although its incidence has been rising over the past decade, penile cancer (PeCa) remains a rare malignancy, accounting for less than 1% of all cancers in men. PeCa is diagnosed in approximately 0.1-1 per 100.000 men annually in Western countries [1]. Its rare incidence represents a challenge for physicians, especially for those who lack specific expertise [2]. However, even with appropriate treatment, PeCa remains an aggressive disease, with more than one third of patients not surviving beyond five years, especially due to delay in diagnosis [3]. Prognosis is strongly stage-dependent: the 5-year overall survival (OS) rate is approximately 80% for patients with localized disease, but falls sharply to 9% for those with distant metastases [4, 5]. Therefore, early diagnosis followed by proper treatment is crucial [6, 7]. In this regard, limited recognition and inadequate knowledge of early signs and symptoms have been reported as possible contributors of delayed diagnosis [6]. Moreover, cultural barriers surrounding discussions of genital and sexual health may further contribute to this delay, even in high-income countries [8].

Finally, the lack of knowledge and awareness of PeCa among patients might cause additional delays [9]. The rarity and complexity of PeCa management along with limited evidence-based recommendations lead to suboptimal treatment outcomes [10]. As such, patients' care benefit from an improvement of the referral system [11]. Therefore, examining the shortcomings in referral pathways – from the initial clinical presentation to definitive surgical management at a tertiary center – is essential for identifying areas for improvement and enhancing the management of care.

MATERIAL AND METHODS

Study population and variables definition

This retrospective study aimed to assess referral pathways and the time interval between the initial appearance of disease and primary surgical treatment at our tertiary center in patients with PeCa. Data from our prospectively maintained database was analyzed, focusing on those patients who received definitive surgical treatment and were either referred to or directly seen at our center. We excluded those who had undergone prior surgical treatment elsewhere and were referred due to disease recurrence, or those receiving systemic therapy, as well as those with incomplete timeline data (N = 19). Patients who had previously received procedures such as biopsy, laser therapy, or topical treatments were not excluded. All subjects underwent a comprehensive medical history assessment, including the timing of disease onset, prior management, and consultation history with GP, and SP. Additional data were collected on clinically relevant comorbidities, as scored with the Charlson Comorbidity Index (CCI) [12], as well as clinicopathologic characteristics such as tumor staging, grading, lymphovascular invasion (LVI) and human papilloma virus (HPV) status. Disease staging was based on data from a physical examination and cross-sectional imaging, either computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)-CT as per international guidelines [13]. Nodal staging was performed with dynamic sentinel node biopsy (DSNB) in patients with cN0 disease from year 2022, while a modified inguinal lymphadenectomy was used as surgical staging method before. Surgical treatments were categorized as conservative - namely circumcision, wide local excision, partial or total glansectomy and partial penectomy - and radical, including subtotal (removal of corpora until at the scrotum) or total penectomy (complete removal of corpora to the pubic bones). Data on oncological outcomes, including local or distant recurrence, as well as survival status were collected. Referral timelines were mapped and correlated with disease stage, surgical approach and oncological outcomes to identify potential areas for improvement. Referral pathways and time to referral were assessed for all patients from initial disease appearance to treatment at our center. Additionally, based on the overall median time from initial penile lesion appearance to surgical treatment at our center, we grouped the whole cohort into: Group 1, patients who received surgical treatments within 12 months; and, Group 2, patients who received surgical treatments after 12 months of disease presentation.

Statistical analyses

We used descriptive statistics to detail the demographic and clinic-pathologic characteristics of the whole cohort. Median and interquartile range (IQR) or frequency and proportion were reported for continuous or categorical variables, respectively. Mann-Whitney and Chi-square tests were used to compare the statistical significance of differences in the distribution of continuous or categorical variables between the two groups of patients, respectively. Second, OS and recurrence free survival (RFS) were calculated using the Kaplan-Meier method. Third, multivariable (MVA) logistic regression models were fitted to identify potential factors associated with local recurrence among primary infertile men. The MVA model was built by considering potential confounders. Fourth, alluvial plot was used to further illustrate different scenarios in the managements of PeCa.

All statistical tests were two-sided with a significance value set at 0.05. The analyses were conducted using R (2024), a language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria.

Study approval

Data collection followed the principles outlined in the Declaration of Helsinki. All patients signed an informed consent agreeing to provide anonymous information for future studies. The Institutional Review Board approved the study (Prot. 2014 Observational Study on Outpatients).

RESULTS

Descriptive characteristics for the whole cohort of patients (N=48) are listed in ***Table 1***. Patients followed distinct referral pathways; of those, 13 (27%) patients were referred through the GP, SP, and our center with a median (IQR) time of 13.9 months (9.7-20.4); 8 (17%) patients were directly referred by the GP to our center and the median time was 18.2 months (9.1-26); 10 (21%) patients were first assessed by the SP [7 (70%) general urologist and 3 (30%) general dermatologist] and then referred to our center with a median time of 6.8 months (6.1-10.5); and, 17 (36%) patients were initially assessed in our center after a median time of 14.3 (11-24.8) months from disease appearance, respectively. The alluvial plot depicts the four different clinical pathways patients followed prior to management at our tertiary center (***Figure 1***). The overall median (IQR) time from initial penile lesion appearance to surgical treatment at our center in the overall cohort was 12.4 (6.8-25.4) months. Of all, Group 1 consisted of 28 (58.3%) patients, while Group 2 of 20 (41.7%) patients. Overall, pT stage, LVI and risk of recurrence were significantly lower in Group 1 (all P ≤0.02), while conservative surgical approaches were significantly higher (P <0.01) as compared with Group 2. ***Table 2*** reports logistic regression analysis testing predictors of local recurrence. At MVA model, delayed surgery (≥ 12 months) was identified as a significant predictor of local recurrence (OR=4.28, P=0.03), after counting for LVI, pT2-3 and cN+. At Kaplan-Meier analysis, the 2-year RFS (IQR) rates were lower in Group 2 as compared to Group 1 [33.8% (14.6-78.2) vs. 84% (68.8-100), P=0.006] (***Figure 2***). The 2-year OS rates were 87.7% (73-100) vs. 67.2% (49.7-90.9) for Group 1 and Group 2, respectively (P=0.09) (***Figure 3***).

DISCUSSION

This study highlights critical gaps in the current management of PeCa within a high-income country healthcare system. Unlike other countries where national networks and referral systems for rare cancers are well established, our country currently lacks a defined pathway for PeCa management [14–16]. No regulations exist to mandate how and when patients should be referred from primary care or community urology practices to specialized centers. Furthermore, socio-demographic aspects, social stigma, fear, and poor awareness of risk factors (i.e., HPV infection, poor hygiene practices, and other intersectional factors like low socioeconomic status and nonmetropolitan area), combined with the lack of awareness of genital conditions among non-specialist doctors, has led to significant delays in diagnosis and surgical treatment [17–19]. As a result, patient management is highly variable, largely dependent on individual physician experience, institutional resources, and geographical factors[20]. This jeopardization likely contributes to the significant diagnostic and therapeutic delays observed in our cohort. Even though most SPs are familiar with international guidelines, adherence remains a challenge especially when dealing with the extraordinary nuances of this disease [21, 22]. Advanced diagnostic techniques such as DSNB, which is now considered the gold standard for nodal staging in clinically node-negative patients, are not routinely available [23, 24]. Nor is there consistent integration with advanced body imaging, nuclear medicine, genitourinary pathology, radiation oncology, or sexual counselling services [11, 25, 26]. Similarly, organ sparing surgical techniques — such as glans resurfacing and partial glansectomy — remain underutilized despite being established as oncologically safe and functionally superior alternatives to more radical procedures. On this matter, in their systematic review and meta-analysis, Fallara *et al.* reported a good oncological outcomes (cancer specific mortality between 0% and 18%) in a cohort of 10847 men who underwent penile shaft sparing surgery [27]. Moreover, experiences from other centers confirmed that the implementation of a standardized care pathway for PeCa resulted in higher rate of sparing surgery (79.9% vs. 57.8%, $p < 0.01$) and surgical staging (90% vs. 41%, $p < 0.01$), respectively [28]. Expertise in radical inguinal lymphadenectomy and the management of associated complications is also limited to a few high-volume centers, leaving a large proportion of patients at risk for suboptimal oncological and functional outcomes. As a matter of fact, Matulewicz *et al.* reported that 26.6% and 48.4% of patients who had an indication for inguinal nodal dissection had one performed at community and academic hospitals, respectively (OR 2.29) [14]. This concerning difference in a potentially curative procedure did confirm that academic-driven centralization may play a role in optimizing the management, especially of patients with more advanced disease. Patients are often treated at low-volume institutions, where limited experience impairs adherence to best-practice protocols, negatively impacting survival, recurrence rates, and quality of life. Moreover, poor physician familiarity with the latest international recommendations frequently results in nonuniform and suboptimal management [11, 29]. Showing significant differences in pathological stage, treatment approach, and recurrence rates based on diagnostic delay, our results should serve as a call to action. Raising awareness among primary care physicians, dermatologists, general urologists, and policymakers is crucial to improving early recognition of suspicious lesions and promoting timely referral to specialized centers. Moreover, the establishment of a formal national network of accredited PeCa

centers — with requirements for case volume, access to specialized diagnostic tools, and demonstrated surgical expertise — should be prioritized. Another important action should focus on raising awareness among the general population. Patients and their families need to be educated about the risk factors for PeCa and the importance of regular urological evaluations [7]. In their survey, Kamkari *et al.* showed that among 83 participants, 98% reported either knowing nothing or little about PeCa, and 69% of respondents did not know a person could develop PeCa. Overall, most participants had limited understanding of risk factors and demonstrated misconceptions about symptoms and outcomes [9]. Similarly, Capogrosso *et al.* reported that 58.5% of men seeking help for uroandrologic purposes were not aware that HPV infection could be associated with PeCa [17]. The impact that awareness has on attitudes towards screening and treatment has been well-documented for many other cancers (i.e., prostate, breast, and cervical cancer) [30, 31]. Although a few awareness campaigns have tried to raise attention on the danger of ignoring symptoms, PeCa remains excluded from public health initiatives, and no dedicated screening or prevention programs exist [32, 33]. These latter ones should at least be considered for high-risk individuals, such as uncircumcised men with precancerous lesions and those with a history of HPV infection. The presence of penile lesions is often associated with feeling of shame and fear, as well as psycho-social stigma that initially can lead afflicted individual avoiding medical evaluation. So that, as previously suggested [6, 26], a compound effect of a lack of awareness and the emotional burden of the disease result in a significant delayed diagnosis. The challenges of its initial management and the inappropriate referral further contribute to delay. However, optimizing referral pathways could significantly minimize additional delays and improve timely access to care. While our study is limited by its retrospective design and relatively small sample size, it nonetheless represents an important step in mapping the deficiencies of the current system. It highlights the urgent need for coordinated national efforts to standardize care pathways, improve training, centralize management, and ultimately enhance outcomes for patients affected by this rare but aggressive disease. Thus, the current unstructured approach to PeCa care in our country must be addressed. Our findings support the necessity for national initiatives aimed at developing referral pathways, accrediting specialized centers, promoting educational interventions and preventive counseling about PeCa. Future efforts should focus on constructing an integrated network that ensures timely diagnosis, evidence-based treatment, and optimal outcomes for all patients with PeCa.

CONCLUSIONS

Our study indicates that delayed diagnosis—driven by the rarity and complexity of PeCa, and unclear referral pathways—may contribute to more advanced tumor stage at treatment, lower rates of conservative surgery, and poorer oncological outcomes. Almost half of the patients treated at our center experienced a delay of more than 12 months from the initial appearance of a penile lesion to definitive surgery, with significant consequences on cancer management. Importantly, delayed surgery independently predicted worse RFS, highlighting the urgent need for earlier recognition and timely intervention.

Declarations

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Author Contributions: Conceptualization: FN, GB, and MB. Data curation: FN, AG, ML, MR, EP, FB, AF, MM, and CM. Formal analysis: GB and FN. Supervision: AS and MB. Validation: FM, AS, MB. Writing – original draft: FN and GB. Writing – review & editing: AN, MC, AB, FM, AS, and MB. All other co-authors reviewed the manuscript and participated in the revisions.

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Ethical approval: The Institutional Review Board approved the study (Authorization Protocol URI001-2010, further amended in December 2015 by the Ethic Committee – 'Observational Study on the Quality of Life of Outpatients' NCT06181851).

Competing interests: None.

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Tables

Table 1. Socio-demographic and clinic-pathologic characteristics of the whole cohort (n=48) of men with histologically confirmed diagnosis of PeCa.

Variable	Whole Cohort	< 12 months (Group 1)	≥ 12 months (Group 2)	p-value
Socio-demographic and clinical characteristics				
Number of patients (No.)	48 (100)	28 (58.3)	20 (41.7)	
Age (years)	65 (51-74)			
BMI (kg/m^2)	25.9 (24.3-29.6)			
CCI [mean (SD)]	5 (3-6.3)			
Follow-up (years)	20.7 (9.4-69.2)			
Referral history				
GP>SP>C (No.)	13 (27)			
GP>C (No.)	8 (17)			
SP>C (No.)	10 (21)			
Direct C (No.)	17 (36)			
Time to first medical assessment (months)	3.8 (1-11.9)			
Time to C (months)	12.4 (6.8-25.4)			
Time-to GP>SP>C (months)	13.9 (9.7-20.4)	7 (6.2-8.5)	18.7 (15.5-34.4)	0.01
Time-to GP>C (months)	18.2 (9.1-26)	8.2 (6.1-10.4	26.3 (25.6-28)	0.03
Time to SP>C (months)	6.8 (6.1-10.5)	6.4 (5.4-7.1)	20.7 (17.8-23.7)	<0.01
Time-to directly C (months)	14.3 (11-24.8)	5.7 (4.9-6.6)	19.6 (14-25.9)	<0.01
Type of surgery				
Conservative (No.)	28 (58.3)	21 (75)	7 (25)	<0.01
Radical (No.)	20 (41.7)	7 (35)	13 (65)	
Histology				

Squamous cell carcinoma (No.)	35 (72.9)	20 (57.1)	15 (42.9)	0.8
Others (No.)	13 (27.1)	8 (61.5)	5 (38.5)	
Staging				
cN				
cN0 (No.)	33 (68.8)	19 (57.6)	14 (42.4)	0.87
cN+ (No.)	15 (31.2)	9 (60)	6 (40)	
pT				
IS/1 (No.)	30 (62.5)	22 (73.3)	8 (26.7)	<0.01
2+ (No.)	18 (37.5)	6 (33.3)	12 (66.7)	
pN				
pN0 (No.)	20 (41.7)	12 (60)	8 (40)	0.16
pN+ (No.)	6 (12.5)	1 (16.7)	5 (83.3)	
cM+	1 (2.1)	0 (0)	1 (100)	0.98
Grading				
1 (No.)	11 (20.8)	6 (54.5)	5 (45.5)	0.75
2 (No.)	31 (64.6)	19 (61.3)	12 (38.7)	
3 (No.)	6 (12.5)	3 (50)	3 (50)	
LVI (No.) (Yes)	10 (20.8)	1 (3.6)	9 (45)	<0.001
p16 (No.) (Positive)	10 (20.8)	6 (21)	4 (20)	1
Recurrence (No.) (Yes)	15 (31)	5 (18)	10 (50)	0.02

Values are presented as number (%) or median (interquartile range) vs. mean (standard deviation), as indicated.

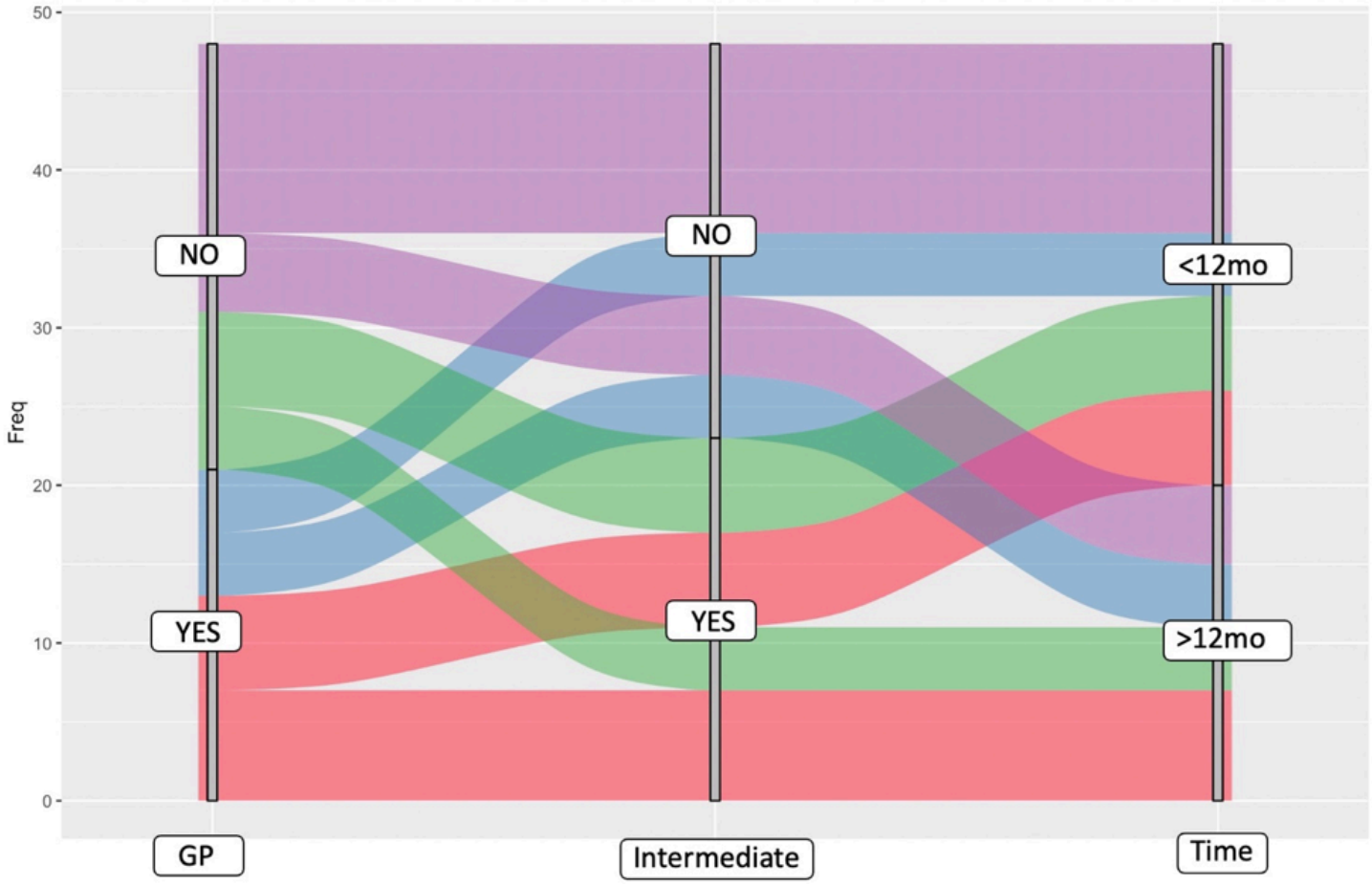
Keys: BMI: Body mass index; CCI: Charlson comorbidity index; GP: General practitioner; SP: Specialist; C: Our center; IS: *in situ*; LVI: Lymphovascular invasion.

Table 2. Multivariable (MVA) logistic regression analysis showing predictors of local recurrence.

	UVA		MVA	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
LVI	2.8 (0.65, 12.2)	0.2	1.35 (0.23, 7.75)	0.7
pT2-3	1.75 (0.49, 6.18)	0.4	0.89 (0.18, 3.8)	0.8
cN+	1.15 (0.29, 4.18)	0.8	1.27 (0.29, 5.28)	0.7
≥ 12 months referral	4.6 (1.29, 18.2)	0.02	4.28 (1.26, 22.5)	0.03

Keys: UVA: Univariable; MVA: Multivariable; LNI: Lymph-node invasion.

Figures



Keys: GP: General practitioner; SP: Specialist; C: Our center.

Figure 1

Alluvial plot shows clinical flows patients followed prior to management at our center (color code: red – GP>SP>C; blue – GP>C; green – SP>C; violet – Directly C).

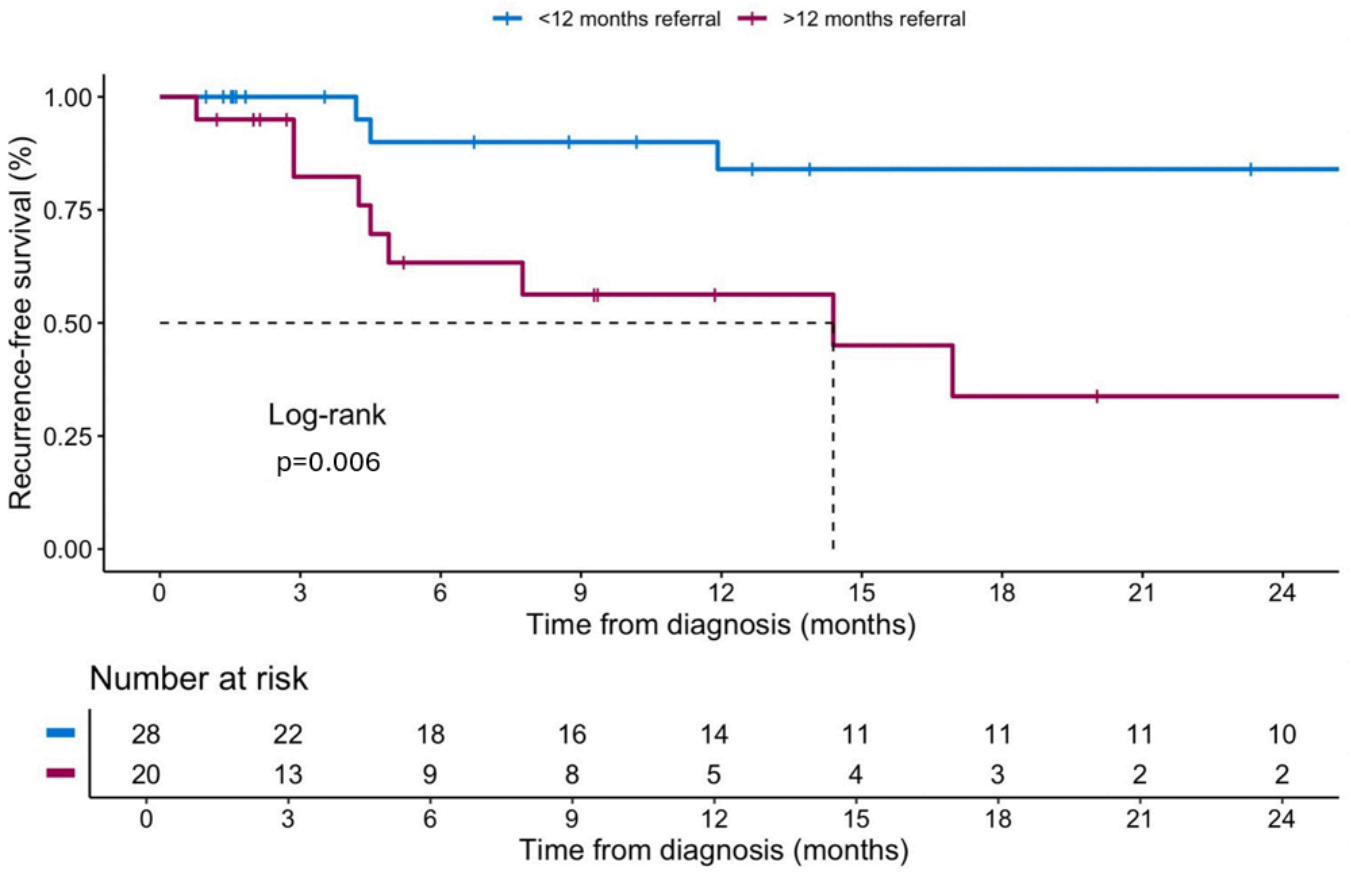


Figure 2

Kaplan-Meier shows recurrence free survival (RFS) based on the time of first diagnosis.

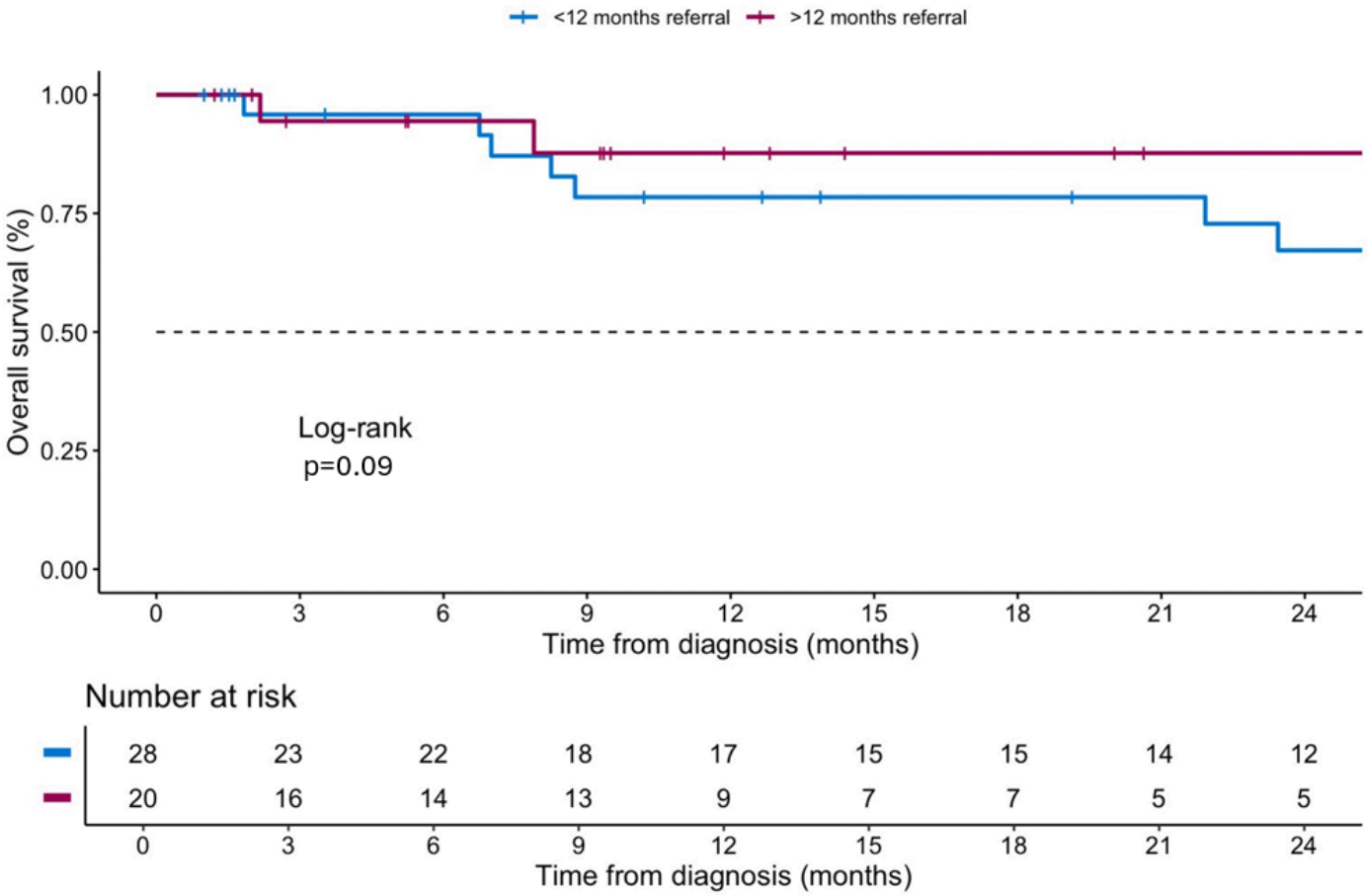


Figure 3

Kaplan-Meier shows overall survival (OS) based on the time of first diagnosis.